REMARKS

Formal Matters

Claims 31-34 and 41-42 are pending in the application. Claims 35-40 are canceled without prejudice to later prosecution. Claim 31 is amended to more particularly point out the subject matter of the invention.

Support for the amendments to claim 31 are found throughout the specification including at the following example recitations. Support for use of the term cardiotrophin-1 is found at page 9, lines 1-13. Support for sequence variants of CT-1 and their preparation is found, for example, at page 9, lines 24-35; at page 26, lines 16-29; page 27, lines 8-19; at page 33, line 26 to page 44, line 14. Support for isolated CT-1 and its biological activity *in vitro* and *in vivo*, including methods of testing for neurotrophic activity, is found, for example, at page 8, lines 18-24 and Figure 4; page 10, lines 10-35; page 26, lines 6-15; at page 26, lines 34-36; page 72, line 22 to page 73, line 9; 74, lines 13-19; page 74, line 29 to page 75, line 2; and page 107, line 24 to page 108, line 26 (Example IV). No new matter is added by the amendments.

Claim Objection - Numbering

The claims were objected to under 37 CFR 1.126 because of an inadvertent error in numbering. Applicants are grateful to the Examiner for correcting the number for the last three claims, which are now claims 40-42.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 33 and 38-40 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking antecedent basis for generically treating ciliary neurons, parasympathetic neurons, peripheral neuropathies involving ciliary neurons or parasympathetic neurons or for treating neurological conditions caused by trauma. The Examiner further states that antecedent basis could not be found in the specification at the sites offered by Applicants. Claims 38-40 have

been canceled without prejudice to later prosecution, rendering their rejection moot. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claim 33 claims a method of increasing survival of a neuron comprising administering to a neuron a survival-promoting amount of a polypeptide having an amino acid sequence identity of at least 70% to SEQ ID NO:3 or SEQ ID NO:8, excluding a rat cardiotrophin-1, wherein the neuron is a ciliary ganglion. Support for the claim is found, for example, at page 8, lines 18-24 (legend for Fig. 4); Fig. 4; page 72, line 22 to page 73, line 9; and Example 4 at page107, line 24 to page 108, line 26. Further support is found at page 3, line 28 to page 4, line 3, where Applicants point out the need for an improvement in treatment for neurological disorders, such as the need for increased neuronal survival such as like that of ciliary neurotrophic factor (CNTF). Applicants then go on to show at page 74, lines 20-28 and in Example 4 (cited above) the usefulness of CT-1 (CHF) *in vitro* and *in vivo* due to its similar behavior to ciliary neurotrophic factor (CNTF) in the CNTF assay.

As a result, claim 33 is fully supported by the specification. Applicants respectfully request withdrawal of the rejection and allowance of the claim.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 31-42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable treatment a neurodegenerative disease state or generic neuronal population with structurally uncharacterized CT-1 polypeptide. The Examiner states, however, that the claims are enabling for a method of increasing survival of motor neurons or embryonic chick ciliary neurons with CT1-1 of SEQ ID NO: 3 or SEQ ID NO:8. Claims 35-40 have been canceled without prejudice to later prosecution, rendering their rejection moot. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claims 31-34 and 41-42, currently pending in the application, claim a method of increasing survival of a neuron comprising administering to a neuron a survival-promoting amount of a polypeptide having an amino acid sequence identity of at least 70% to SEQ ID NO:3

or SEQ ID NO:8, excluding a rat cardiotrophin-1. Support for claiming structural variants of SEQ ID NO:3 or SEQ ID NO:8, as noted above, include recitations in the specification at, for example, page 9, lines 24-35; at page 26, lines 16-29; page 27, lines 8-19; and at page 33, line 26 to page 44, line 14. Structural variants may be readily prepared and tested for biological activity in support of any one of claims 31-34 by one of ordinary skill in the art without undue experimentation.

Support for use of the CT-1 or its biologically active variant is found, for example, at page 3, line 28 to page 4, line 3, where Applicants point out the need for other agents like CNTF for increasing neuronal survival and then go on to show the similarity of CT-1 and CNTF behavior in the CNTF assay supported at page 8, lines 18-24 (legend for Fig. 4); Fig. 4; page 72, line 22 to page 73, line 9; and Example 4 at page107, line 24 to page 108, line 26; and at page 3, line 28 to page 4, line 3, where Applicants point out that CT-1 may be used for neuronal survival. One of ordinary skill in the art would not be required to perform undue experimentation to reach Applicants' invention given this guidance in the specification. As a result, claim 31 is fully supported in the specification.

Claims 32-34, which depend from claim 31, claim the above method wherein the neuron is a peripheral nervous system neuron, a ciliary ganglion, or a motor neuron, respectively. Support for these claims is found at the above recitations as well as at, for example, page 4, lines 1-2, and 9; page 42, line 19 to page 25, line 12; page 73, lines 14-15; and page 75, lines 4-5 (for peripheral neurons); at page 24, lines 22-23, and 33; page 25, line 2; page 73, lines 14-15; page 74, lines 30-32; and page 75, lines 4-5 (for motor neurons); and at page 3 line 33; page 8 lines 18-24 (and Fig. 4); page 12, lines 1-2; page 26, lines 8-9 and 34-35; page 72, line 22 to page 73, line 9; page 74, line 20-28; and page 107, lines 24 to page 108, line 26 (Ex. IV) (for ciliary ganglia).

Claims 41 and 42 claim the addition of a second neurotrophic factor such as 1GF-1, CNTF, NGF, BDNF, NT-3, and NT-4 for increasing neuronal survival. Support for the claims is provided in claim 31, at page 10, lines 4-9; page 30, lines 23-29; and at page 75, lines 8-10.

Thus, claims 31-34 and 41-42 are fully supported by the specification. Withdrawal of the rejection under Section 112, first paragraph is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 34 and 41 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

In the Office Action at page 5, item 4, the Examiner states that it is ambiguous and confusing how treatment of a peripheral neuropathy is envisioned, particularly as it relates to claims 34. Claim 34 claims a method of increasing survival of a neuron (as in claim 31), where the neuron is a peripheral nervous system neuron (claim 32), such as a motor neuron (claim 34). "All nerve cells or parts of nerve cells which lie outside the skull or vertebral column are known collectively as the peripheral nervous system" (see "Human Physiology: The Mechanisms of Body Function," 2d ed., Vander, A.J. et al., eds. (1975), page 147, enclosed). Thus, a motor neuron according to claim 34 is readily understood to part of the peripheral nervous system. Claim 34 is, therefore, not indefinite and withdrawal of the rejection is respectfully requested.

According to the Examiner, the phrase "therapeutically effective amount" is allegedly unclear and it is suggested that the phrase "for increasing neuronal survival" be added to claim 41. While Applicants traverse the rejection because the administration of survival-promoting amounts of the additives is readily understood, Applicants have added the phrase merely to advance prosecution of the claims. The rejection is obviated and withdrawal of the rejection is respectfully requested.

SUMMARY

Claims 31-34 and 40-42 are pending in the application. Claims 35-40 are canceled without prejudice to later prosecution. Claims 31, 41 and 42 are amended merely to correct inadvertent errors in numbering, to more particularly point out the subject matter of the invention; or merely to advance prosecution of the claims. The amendments add no new matter. The rejections under Sections 112 first and second paragraph has been overcome. Withdrawal of the rejections and allowance of the claims is respectfully requested.

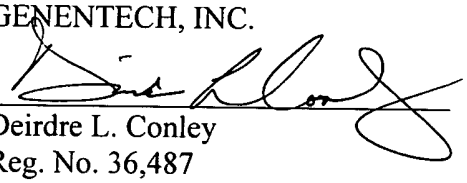
If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

This response/amendment is timely submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,

GENENTECH, INC.

Date: March 4, 2003

By: 

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PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 31 40-42 are amended as follows, wherein strikeout in brackets [~~00~~] indicates deleted terminology and underling [00] indicates added terminology. Claims 35-40 are canceled without prejudice to later prosecution. Please note that although claim 40 is canceled, the amendment of the number of claim 40 (from "38" to "40") is shown here.

31. A method of increasing survival of a neuron, comprising administering [to a neuron] a survival-promoting amount of [~~cardiotrophin-1 to the neuron~~][an isolated biologically active polypeptide having an amino acid sequence identity of at least 70% to SEQ ID NO: 3 or SEQ ID NO:8, but not a rat cardiotrophin-1].

32. The method of claim 31, wherein the neuron is a peripheral nervous system neuron.

33. The method of claim 32, wherein the neuron is a ciliary ganglion.

34. The method of claim 32, wherein the neuron is a motor neuron.

Renumber the last three claims as claims 40-42.

[~~38~~][40]. The method of claim 35, wherein the neurological disorder is caused by trauma.

[~~39~~][41]. The method of claim 31 further comprising administering a therapeutically effective amount of a second neurotrophic factor [for increasing neuronal survival].

[~~40~~][42]. The method of claim 39, wherein the second neurotrophic factor is selected from the group consisting of IGF-1, CNTF, NGF, BDNF, NT-3, and NT-4.

Please cancel claims 35-40 without prejudice to later prosecution.

Clean Set of All Pending Claims

March 4, 2003

31. (Amended) A method of increasing survival of a neuron, comprising administering to a neuron a survival-promoting amount of an isolated biologically active polypeptide having an amino acid sequence identity of at least 70% to SEQ ID NO: 3 or SEQ ID NO:8, but not a rat cardiotrophin-1.

32. (Reiterated) The method of claim 31, wherein the neuron is a peripheral nervous system neuron.

33. (Reiterated) The method of claim 32, wherein the neuron is a ciliary ganglion.

34. (Reiterated) The method of claim 32, wherein the neuron is a motor neuron.

41. (Amended) The method of claim 31 further comprising administering a therapeutically effective amount of a second neurotrophic factor for increasing neuronal survival.

42. (Amended) The method of claim 39, wherein the second neurotrophic factor is selected from the group consisting of IGF-1, CNTF, NGF, BDNF, NT-3, and NT-4.

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HUMAN PHYSIOLOGY
THE MECHANISMS OF BODY FUNCTION

SECOND EDITION

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THE MECHANISMS OF BODY FUNCTION

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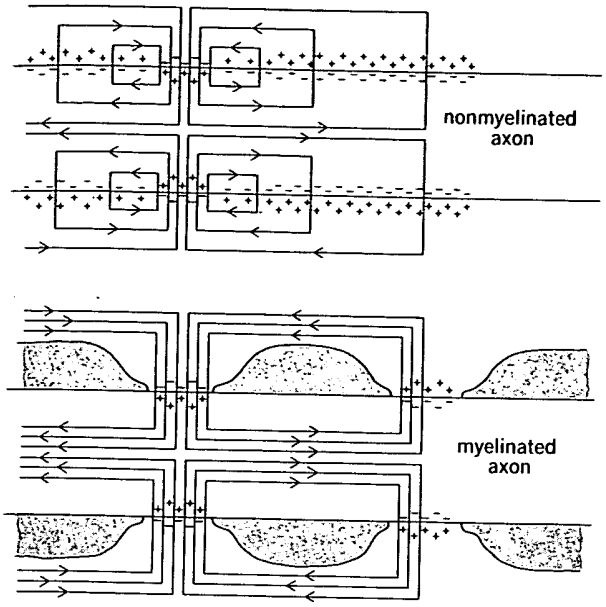

FIGURE 6-18
Ion current flows during an action potential in a nonmyelinated and a myelinated axon.

SECTION B
PHYSIOLOGICAL ACTIVITIES OF NEURONS

Functional anatomy of neurons

The basic unit of the nervous system is the individual nerve cell, or *neuron*. (However, only 10 percent or so of the cells in the nervous system are neurons; the remainder are glial cells, which probably sustain the neurons metabolically and support them physically.) The human nervous system is thus composed of the neurons and glial cells which make up the brain and spinal cord as well as the many nerve processes which pass between these two structures and the receptors, muscles, or glands which they innervate. The brain and spinal cord, together forming the *central nervous system*, are protected by being housed within the bony skull and vertebral column (backbone). All nerve cells or parts of nerve cells which lie outside the skull or vertebral column are known collectively as the *peripheral nervous system*.

The neuron can be divided structurally into three parts, each associated with a particular function (Fig. 6-21): (*1*) the dendrites and cell body, (*2*) the axon, and (*3*) the axon terminals. The *dendrites* form a series of highly branched cell outgrowths connected to the cell body and may be looked upon as an extension of the cell membrane of the neuron cell body. The dendrites and cell body are the site of most of the specialized junctions with other neurons through which signals are passed to the cell. Moreover, the cell body contains the nucleus and many of the organelles involved in metabolic processes and is responsible for maintaining the metabolism of the neuron and for its growth and repair.

The *axon*, or *nerve fiber*, is a single long process extending from the cell body, usually considerably longer than the dendrites. The first portion of the axon plus the part of the cell body where the axon is joined is known as the *initial segment*. The axon can give off branches called *collaterals* along its course, and near the end it undergoes considerable branching into numerous *axon terminals*, the last part of which is enlarged and is responsible for transmitting a signal from the neuron to the cell contacted by the axon terminal. Neurons assume many different shapes, depending upon their role (Fig. 6-22), and sometimes the axons and dendrites are hard to distinguish; for example, the long process between the receptors and cell body of an afferent neuron (Fig. 6-22) is technically a dendrite since it conducts action potentials toward the cell body, yet it looks like an axon and is, in fact, often called an axon or nerve fiber.

Yet, regardless of their shape, neurons can be divided into three classes: afferent neurons, efferent neurons, and interneurons (Fig. 6-23). Afferent and efferent neurons lie largely outside the skull or vertebral column, and interneurons lie within the central nervous system.

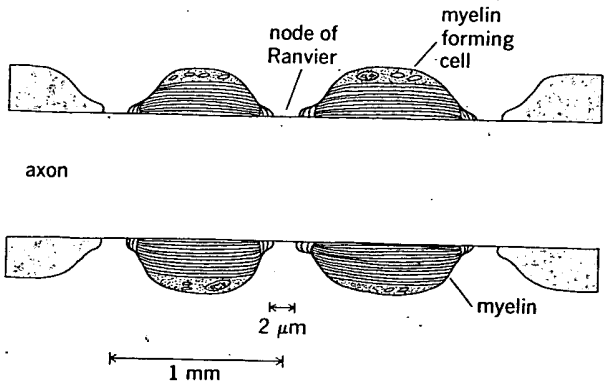

FIGURE 6-19
Structure of a myelinated axon. The surface of the axon is exposed to the extracellular fluid at the nodes of Ranvier.